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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/777,543	02/12/2004	Harold M. Bates	C015043/0174944	9840

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EXAMINER	
FOSTER, CHRISTINE E	
ART UNIT	PAPER NUMBER
1641	
MAIL DATE	DELIVERY MODE
11/25/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,543	BATES, HAROLD M.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2008 and 27 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,12,13,15-20,22-29,33,34,36-41 and 43-88* is/are pending in the application.

4a) Of the above claim(s) *43-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,12,13,15-20,22-29,33,34,36-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :2/12/04, 6/18/04, 6/23/04, 11/10/05, 5/26/06, 8/29/06, 9/5/06, 11/8/07, 5/9/08, 5/28/08, 7/27/09.

DETAILED ACTION

1. Please note that the Examiner in your application has changed. The new Examiner, Christine Foster, may be reached at 571-272-8786.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/9/2008 and as corrected on in the reply of 7/27/2009 has been entered.

3. Claims 1, 12-13, 22, and 33-34 were amended. Claims 9, 11, 21, 30, 32, and 42 were canceled. Accordingly, claims 1-8, 12-13, 15-20, 22-29, 33-34, 36-41, and 43-88 are pending in the application, with claims 43-88 currently withdrawn. Claims 1-8, 12-13, 15-20, 22-29, 33-34, and 36-41 are subject to examination below in light of the elected species of **OxLDL** as the atherogenic protein and of **C-reactive protein** as the acute phase reactant.

Rejections Withdrawn

4. Applicant's arguments, see pages 22-32, filed 5/9/2008, with respect to the rejection(s) of claim(s) 1-8, 12-13, 15-20, 22-29, 33-34, and 36-41 under § 101, § 112, 1st paragraph, and § 112, 2nd paragraph have been fully considered and are persuasive. Therefore, the rejections have been

withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the prior art references discussed in detail below.

Priority

5. The present application was filed on 2/12/2004. No priority claims have been made.

Information Disclosure Statement

6. The information disclosure statements filed **11/8/2007** and **8/7/2009** fail to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; **(3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials**; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statements have been placed in the application file, but the information referred to therein has not been considered.

Specifically, it is acknowledged that Applicant has submitted two pages of remarks on 11/8/2007 under the heading "Eighth Supplemental Information Disclosure Statement". Three pages of remarks under the heading "Thirteenth Supplemental Information Disclosure Statement" were also submitted on 8/7/2009. However, no forms PTO-1449 or PTO/SB/08a

were apparently included. These submissions do not constitute compliant information disclosure statements for the reasons indicated in boldfaced type above.

Specification

7. The disclosure is objected to because of the following informalities: on page 22, line 23, "CPR" should apparently read --CRP--.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-8, 12-13, 15-20, 22-29, 33-34, and 36-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holvoet et al. (U.S. 6,309,888 B1) in view of Valkirs et al. (U.S. 2003/0109420 A1).

Holvoet et al. teach methods for detecting the presence of coronary artery disease by testing samples to determine the level of OxLDL, the level of MDA-modified LDL, and the level of a third marker such as troponin. See especially the abstract; column 1, lines 5-13; column 4, line 1 to column 8, line 45. OxLDL and MDA-modified LDL are atherogenic proteins as defined in the instant specification (page 21, line 22 to page 22, line 5).

Holvoet et al. further teach that OxLDL and MDA-modified LDL can be measured via immunological assays that employ the monoclonal antibodies mAb-4E6, mAB-1H11, or mAb-8A2 (column 4, lines 44-53; column 12, line 29 to column 15, line 33; column 17, lines 39-57; and the claims).

In addition to detecting the presence or absence of coronary artery disease (CAD), the methods of Holvoet et al. can also distinguish between non-acute CAD and acute CAD, where non-acute CAD means that the patient has either asymptomatic CAD or stable angina (column 3, lines 4-13; column 4, lines 1-15 and line 64 to column 6, line 66). These methods may be conducted as part of a screening or as part of a routine physical examination and may be performed on patients who are **asymptomatic** for coronary artery disease (see especially at column 6, lines 47-66).

It is noted that instant claim 1 recites "detecting whether the patient has asymptomatic coronary artery disease" (preamble and step (c)). As discussed above, Holvoet et al. make clear that their methods can be used to diagnose the absence of coronary artery disease, as opposed to the presence of non-acute coronary artery disease (either asymptomatic CAD or stable angina). As such, the methods of Holvoet et al. read on the claimed step of detecting *whether* the patient has asymptomatic CAD since in verifying that CAD is absent, the presence of asymptomatic CAD, stable angina, and acute CAD are being ruled out.

To assess whether marker levels in the patient samples are clinically significant, Holvoet et al. teach the use of predetermined cut points or threshold levels (i.e., cut-points), above which the markers are considered to be indicative of coronary artery disease. See column 4, lines 15-30;

column 5, lines 7-63; column 19, lines 15-41; claim 1; and especially at column 8, line 42 to column 10, line 37 and at column 19, lines 33-40.

Holvoet et al. further illustrate measuring levels of C-reactive protein (see column 17, line 64 to column 18, line 2; column 19, lines 15-24; column 21, lines 61-62; column 22, lines 51-53; and Tables III and VI-IX), which is an acute phase reactant as disclosed instantly (specification, page 22, lines 22-23). Holvoet et al. observed that levels of C-reactive protein were elevated in subjects known to have various types of coronary artery disease as compared with control subjects (see Table III in particular).

Although Holvoet et al. thereby measured levels of the acute phase reactant C-reactive protein, this was apparently done as a means of validating the efficacy of OxLDL and MDA-modified LDL as diagnostic markers, by comparison with other known markers such as C-reactive protein.

As such, the teachings of Holvoet et al. differ from the claimed invention in that the reference does not specifically teach using levels of an acute phase reactant as part of their methods to detect the presence, absence, and/or stage of coronary artery disease in a patient.

In addition, with respect to claim 22, Holvoet et al. fail to explicitly teach providing information to a medical professional as recited in the preamble and in steps (c)-(d).

However, it was known in the art at the time of the invention that measuring multiple markers of a disease in a "multimarker" approach may result in improved assay when performing clinical assays. For example, Valkirs et al. teach that a plurality of markers can be combined in a "multimarker" strategy to increase the predictive value of an analysis (diagnostic or prognostic) in comparison to that obtained using the markers individually [0017], [0107], [0184].

Therefore, because OxLDL, MDA-modified LDL, and C-reactive protein were all recognized by Holvoet et al. to be markers correlated with the presence and/or stage of coronary artery disease, it would have been obvious to one of ordinary skill in the art to also measure C-reactive protein levels and to use this information when detecting whether an asymptomatic patient has coronary artery disease according to the methods of Holvoet et al. In particular, it would have been obvious to also measure levels of C-reactive protein in asymptomatic subjects and to compare the observed levels with predetermined cut points or threshold levels in the same manner taught by Holvoet et al. for OxLDL and MDA-modified LDL, so as to assess the presence, absence, and/or stage of asymptomatic coronary artery disease in the patient. Put another way, when detecting C-reactive protein in addition to OxLDL and MDA-modified LDL as part of the multimarker strategy of Valkirs et al., it would have been obvious to employ cut points for each marker being assayed (e.g., a first cut-point for OxLDL, a second cut-point for C-reactive protein, etc.) and to compare the subject's observed marker levels with these predetermined levels in the same manner illustrated by Holvoet et al. for their multimarker assay, in order to properly interpret the results of the assay.

One would be motivated to combine the reference teachings in this manner in order to improve the predictive value of the diagnostic assessment, based on the teachings of Valkirs et al. that a plurality of markers of a disease can be combined together to improve analysis as compared to the markers individually.

With respect to the steps of "providing information to a medical professional" as in claim 22, it is noted that Holvoet et al. discuss how their methods, which use multiple tests together, rapidly provide all the information needed by the clinician about the patient to permit possible

life-saving treatment (column 6, line 48 to column 7, line 4; column 10, lines 38-63). The reference further discusses how a physician would use the results of the methods for diagnosis and treatment (ibid). For example, when the methods indicate that the patient has non-acute coronary artery disease, the physician may take action such as recommending a change in life style, prescribing appropriate medication, etc. (column 6, lines 48-66).

Therefore, although Holvoet et al. do not explicitly disclose a step in which the results of the method are provided to a medical professional to then use in determining whether the individual has coronary artery disease, the reference nonetheless clearly conveys that the results of their methods can be used by a physician in order to diagnose the presence, absence, and/or stage of coronary artery disease; as well as to administer appropriate treatment. When taken together with the general knowledge in the art, therefore, it would have been obvious to one of ordinary skill in the art to provide the results of the method of Holvoet et al. and Valkirs et al. to a physician so that the patient could be diagnosed and appropriately treated. For example, it would have been obvious to conduct the method in a clinical laboratory setting and to communicate the patient's test results to their physician in accordance with routine medical care practices.

With respect to claims 3, 18, 24, and 39, Holvoet et al. teaches detection of OxLDL whose apo B-100 moieties contain at least 60 substituted lysine residues (column 12, lines 55-65).

With respect to claims 6, 8, 15, 17, 19, 27, 29, 36, 38, and 40, which refer to detection of HDL as an anti-atherogenic protein, it is noted that Holvoet et al. also measured levels of HDL cholesterol (column 17, line 58 to column 18, line 6; and Tables III and V-IX). As such, it would

have been further obvious to one of ordinary skill in the art to also measure HDL levels when performing the methods of Holvoet et al. and Valkirs et al., since the teachings of Holvoet et al. indicate that HDL is a marker that is normally measured when assessing coronary artery disease. In addition, it is noted that the data of Holvoet et al. demonstrate that HDL levels are correlated with the presence of coronary artery disease (Table III and column 20, lines 28-67). When taken together with the teachings of Valkirs et al. as discussed above, it would also have been obvious to measure HDL in addition to the markers discussed above when assessing subjects for the presence, absence, and/or stage of coronary artery disease. As above, one would be motivated to do this in order to improve the predictive value of the diagnostic assessment, based on the teachings of Valkirs et al. that a plurality of markers of a disease can be combined together to improve analysis as compared to the markers individually.

Response to Arguments

10. Applicant's arguments with respect to claims 1-8, 12-13, 15-20, 22-29, 33-34, 36-41 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

11. No claims are allowed.

12. Applicant is advised that should claim 2 be found allowable, claim 13 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight

difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641